



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 177512

TO: Anand Desai
Location: 3b69 / 3c70
Art Unit: 1653
Thursday, February 09, 2006

Case Serial Number: 10 / 639999

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Search Notes

ubiquitylation and determining whether the compound affects Type I-III **N-end rule ubiquitylation**.

Making a pharmaceutical formulation containing one or more active compounds identified by the method of (7) comprises forming a mixture comprising the protein or an activated fragment of the protein having an exposed **N-degron**, an **N-end**

rule ubiquitylation system, one or more candidate compounds and, optionally, a proteasome system, detecting N-rule ubiquitylation and/or proteasome-mediated degradation of the compound, identifying one or more active compounds from the one or more candidate compounds and incorporating at least one of the one or more active compounds into a pharmaceutical formulation comprising at least one active compound and a carrier. The one or more active compounds are inhibitors or promoters of **N-end rule**

ubiquitylation. The one or more active compounds are naturally occurring. The one or more candidate compounds are selected from a compound library of FDA approved drugs. Modulating N-rule ubiquitylation of a protein comprises administering one or more active compounds of the methods of (7) - (9). Changing the level of a protein, e.g. aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMG17, HSPC144, CDC6 (in vitro, in vivo or ex vivo) comprises administering an amount of an active compound identified by the method of (7). Creating a modified protein by modifying a protein of interest to change its susceptibility to N-end rule degradation, the protein is aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMG17, HSPC144, CDC6 comprises decreasing the susceptibility of the protein to N-end rule degradation by modifying a protease cleavage site to prevent protease cleavage at the site, where cleavage at the protease cleavage site leads to exposure of an **N-degron**, increasing the susceptibility of the protein to N-end rule degradation by introducing a protease cleavage site for a known protease, where cleavage at the protease cleavage site leads to exposure of an **N-degron** and decreasing the susceptibility of the protein to N-end rule degradation by modifying a protease cleavage site that when cleaved exposes an **N-degron** so that, after modification, the C-terminal product of the protease cleavage is not recognized by an N-end rule E3 ligase. The method further comprises expressing the modified protein in a cell. The cell does not express the protein of interest. Generating a phenotypic cell line or animal comprises generating a clone for a mutated form of a protein, e.g. aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMG17, HSPC144, CDC6 or their fragments or derivatives, the mutated protein having a mutated protease cleavage site and/or **N-degron**, thus, modulating the susceptibility of the protein to **N-end rule ubiquitylation**, using the vector to transfect the cell line or to generate a transgenic animal by homologous or non-homologous recombination and detecting at least one phenotypic change relative to a control cell line or animal expressing the non-mutated form of protein.

=> d his

(FILE 'HOME' ENTERED AT 06:14:48 ON 09 FEB 2006)

FILE 'HCAPLUS' ENTERED AT 06:15:24 ON 09 FEB 2006

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L1      1 US2004137597/PN OR (US2003-693999# OR US2002-422448# OR US2003-
      E DAVYDOV I/AU
L2      288 E3-17,E19-22
      E KENTEN J/AU
L3      50 E3-7
      E BIEBUYCK H/AU
L4      68 E3-7
      E OBEROL P/AU
      E OBEROI P/AU
L5      5 E3-4
L6      21 ((MESOSCALE OR MESO (1W)SCALE) (L)TECH?)/CS,PA

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FILE 'REGISTRY' ENTERED AT 06:20:01 ON 09 FEB 2006

FILE 'HCAPLUS' ENTERED AT 06:20:03 ON 09 FEB 2006

L7 TRA L1 1- RN : 29 TERMS

FILE 'REGISTRY' ENTERED AT 06:20:03 ON 09 FEB 2006

L8 29 SEA L7
L9 3885 ?UBIQUITIN/CNS
L10 41 APRATAXIN/CNS

FILE 'HCAPLUS' ENTERED AT 07:14:37 ON 09 FEB 2006

L11 9 L10
L12 30 APRATAXIN
L13 33 L11-12
L14 2119 PROTEIN#/CW (L) (SLP# OR SYNAPTOTAGMIN (1W)LIKE (1W)PROTEIN# OR
L15 608 PROTEIN#/CW (L) (CULLIN3 OR CULLIN 3 OR CDC53 OR CDC 53 OR CULLI
L16 3 PROTEIN#/CW (L) (HSPC144 OR HSPC 144)
L17 25 PROTEIN#/CW (L)APRATAXIN
E TAU FACTOR/CT
E E3+ALL
L18 3460 E2+OLD
E TRANSFERRIN/CT
E E3+ALL
E E2
E E3+ALL
L19 227 E7+OLD,NT (L)TAU
L20 15063 ?UBIQUITIN
L21 5 L13-14,L16-17 (L) L19-20
L22 167 L15,L18,L19 (L) L20
L23 111 L13-14,L16-17 AND L9
L24 409 L15,L18,L19 AND L9
L25 15 L21-22 (L) CONJUGAT?
L26 165 L23-24 AND CONJUGAT?
L27 1 L25-26 AND L1-6
L28 127 N (L)END (L)RULE?(L)UBIQUIT?
L29 2 L25-26 AND L28
L30 28 N (L)DEGRON
L31 1 L30 AND L25-26
L32 1 L29,L31 AND L1-6
L33 1 L29,L31 NOT L32
L34 1 L31-33 AND L1-6
L35 2 L31-33 AND L11-30
L36 2 L34-35

FILE 'MEDLINE' ENTERED AT 09:06:58 ON 09 FEB 2006

L37 19 N (1W) (DEGRON OR END (1W)RULE (1W)UBIQUIT?)

FILE 'EMBASE' ENTERED AT 09:12:20 ON 09 FEB 2006

L38 19 L37

FILE 'BIOSIS' ENTERED AT 09:16:13 ON 09 FEB 2006

L39 27 L38

FILE 'WPIX' ENTERED AT 09:20:58 ON 09 FEB 2006

L40 6 L37
SEL AN 2 L40
L41 1 E1 AND L40

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